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Authors: Kate White, Mike Targett, John Harris

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Review

Gainfully employing descending controls in acute and chronic pain management

Kate White [a,*], Mike Targett [a], John Harris [b]

[a] *School of Veterinary Medicine and Science, University of Nottingham, Sutton Bonington, Loughborough, LE12 5RD*
[b] *School of Biosciences, University of Nottingham, Sutton Bonington, Loughborough, LE12 5RD*

[*]Corresponding author. Tel.: +44 115 9516096
E-mail address: kate.white@nottingham.ac.uk

Highlights

- Descending controls alter the gain in the processing of nociceptive inputs
- The monoamines have major and complex modulatory roles in the descending controls
- Understanding descending modulation is essential for development of new analgesics

Abstract

Specific primary afferent fibres termed nociceptors are responsible for transmitting nociceptive information. Centrally the axonal terminals of these fibres synapse with secondary projection neurones in the spinal dorsal horn to transmit nociceptive information to the higher centres in the brain. Irrespective of the presence or absence of nociceptive inflow the activity of dorsal horn neurones is modulated by, amongst other things, local interneurones and descending midbrain and brainstem networks which can inhibit or facilitate dorsal horn transmission. These pathways therefore set the threshold for information inflow to the CNS. This review article summarises the anatomy, physiology and pharmacology particularly of these descending inhibitory and facilitatory pathways and explains why the study of descending

modulation is essential if we are to develop more efficacious interventions for treating pain and relieving suffering.

Keywords: Analgesia; DNIC; Nociception; Pain modulation

Introduction

Much of what we know about pain to date has been discovered utilising various pharmacological and neurophysiological techniques in animal models and these discoveries have more recently been confirmed with genomics and advanced imaging. Nociceptors transmit information from the periphery to the dorsal horn of the spinal cord. Here the axonal terminals synapse with secondary projection neurones which then transmit nociceptive information to higher centres in the brain. The activity of these dorsal horn neurones is modulated by, amongst other things, local interneurones and descending midbrain and brainstem networks which can inhibit or facilitate dorsal horn transmission. These pathways therefore set the threshold for information inflow to the CNS. Neurophysiological modalities, such as electroencephalography (EEG), bispectral index (BIS), nociceptive withdrawal reflexes (NWRs) and somatosensory evoked potentials (SEP) have been used to study both afferent ascending and descending pain pathways and cortical representation of pain (Murrell and Johnson, 2006). Whilst some may argue that it is preferable to use behavioural outcome measures in conscious animals in order to better capture behavioural/learned and homeostatic mechanisms in response to a noxious insult, anaesthetized animal models can reduce the subjectivity and bias associated for example with quantifying a withdrawal response. Nonetheless, the emphasis in both anaesthetized and conscious patients, particularly in the study of chronic pain, should be that an appropriate parameter is measured (Mogil and Crager, 2004), but we are still some way off having a validated set of tools for testing all components of the pain experience. This review focuses particularly on the anatomy, physiology and

pharmacology of the descending inhibitory and facilitatory pathways highlighting potential targets for pain modulation in animals and man.

Studying pain electrophysiologically

Electroencephalography provides a unique insight into how the nociceptive pathways contribute to pain perception. This technique utilises electrodes placed at various locations on the head producing the summated electrical activity of populations of neurones and glial cells (Murrell et al., 2005; 2008). Electroencephalography has numerous research and clinical applications (Teplan, 2002). The technique can be used in humans and animals to measure anaesthetic depth and antinociceptive effect of different drugs during anaesthesia (Rampil and Matteo, 1987; Johnson and Taylor, 1998). For example in ponies undergoing halothane anaesthesia, lidocaine obtunded the EEG median frequency (F_{50}) change, which is the frequency below which 50% of the power of the EEG is located, that occurred with surgical castration illustrating the use of intraoperative EEG monitoring and examination of F_{50} during application of a noxious surgical stimulus as a tool to investigate the antinociceptive action of different agents (Murrell et al., 2003; 2005). Direct recording of the activity of individual neurones during application of a noxious or non-noxious stimulus can provide information about the intensity, quality, duration and velocity of the stimulus and may involve recording from peripheral afferent sensory fibres or from dorsal horn wide dynamic range (also known as convergent) neurones (Dickenson and Le Bars, 1983; Bee and Dickenson, 2007; Kelly et al., 2012). Recording of NWRs is also an established neurophysiological technique consisting of applying a noxious stimulus, for example to the limb of an animal, and measurement of electromyographic (EMG) activity in muscles contributing to limb withdrawal (Levinsson et al., 1999; Clarke et al., 1992; Clarke and Harris, 2004). The withdrawal response, far from

being a simplistic monolithic reflex, is a modular combination of reflexes to individual muscles arranged in a matrix to best withdraw or remove the limb from the inciting injury (Harris and Clarke, 2003; 2007). NWRs can be used as a direct measure of spinal cord hyperexcitability and thus a biomarker of central sensitization (Harris and Clarke, 2007). Central sensitization is defined as an increase in excitability of neurones in the central nociceptive pathways to normal or subthreshold input (Loeser and Treede, 2008), and is manifest as altered pain sensitivity (Woolf, 2011). In models of persistent pain, central sensitization causes a decrease in the threshold required to elicit an EMG response and is also characterized by enhanced temporal summation of NWRs, which describes an increased perception of pain in response to repetitive painful stimuli; both measures are used to evaluate changes in spinal cord nociceptive processing (Kelly et al., 2013). These techniques are used in rodents during anaesthesia, but NWR thresholds and temporal summation have also been measured in awake and anaesthetized dogs and horses using electrical stimuli to evaluate central sensitization, study the pharmacology of descending controls and characterise antinociceptive effects of analgesic drugs (Peterbauer et al. 2008; Bergadano et al. 2009; Levionnois et al. 2010; Hunt et al. 2016).

The spino-bulbo-spinal loop

A pain experience consists of both a somatosensory component and a psychological, affective component. The term nociception refers to the neural activity in the peripheral and central nervous system caused by a painful stimulus and the term pain itself is used to describe both this and the emotional and autonomic responses to the insult. These different components of pain are processed in separate, discrete areas of the brain. In most cases the nociceptive insult is the cause of pain, but this insult may be absent and its magnitude is not linearly related to the pain that is reported or behaviours that are displayed (Loeser and Treede, 2008). This is, in part, a consequence of a feedback loop between the brain and spinal cord. This spino-bulbo-

spinal loop can alter the extent to which pain signals are amplified or inhibited within the spinal cord.

Painful stimuli are sensed by a diverse range of nociceptor terminals, and initiate action potentials that travel along nociceptive afferents (non-myelinated C fibres or small diameter myelinated A delta fibres) which synapse with nociceptive specific (NS) cells in laminae I-II of the superficial dorsal horn, with a small number terminating deeper in the spinal cord. In contrast transmission of innocuous stimuli is predominantly through large diameter, myelinated A beta fibres which terminate predominately in laminae III-VI, hence within these laminae are proprioceptive neurones responding exclusively to touch. A third class of neurone, known as wide dynamic-range (WDR), can receive input from A delta, A beta or C fibres and responds in a graded manner (i.e. frequency of action potentials) from low through to high threshold noxious input. It is within the spinal cord that substantial transformation and modulation of the nociceptive signal can occur before it ascends to higher centres (Kayalioglu, 2009), due to discrete populations of intrinsic interneurones that can alter responses of NS and WDRs neurones, and astrocytes and microglia are also modulatory, particularly in disease states (Hains and Waxman, 2006; Scholz and Woolf, 2007; Ji et al., 2013). The ascending tracts are usually defined according to where they terminate in the brain (Dostrovsky and Craig, 2013). Briefly, the spinothalamic tract (terminating in the thalamus) integrates the thalamic traffic (and other signals) and is responsible for the discriminative/localisation component of pain via projections to the sensorimotor cortex, insular cortex and the anterior cingulate (Purves et al., 2001; Dum et al., 2009). The other major ascending partner tract is the spinobulbar tract (terminating in both the hindbrain and midbrain regions associated with pain processing) and this conveys the affective/intensity component, and projects to the amygdala and hypothalamus via the parabrachial nucleus (Craig, 2003). This spinobulbar pathway can influence and recruit descending pathways via the periaqueductal grey, pontine locus coeruleus and

rostroventromedial medulla, thereby dictating the output passing through the spinal cord (Benarroch, 2008; Waters and Lumb, 2008)

Anatomy of the descending pathways

One of the most important structures associated with the descending pain control system is the region located around the aqueduct of Sylvius known as the periaqueductal grey matter (PAG) (Behbehani, 1995; Keay and Bandler, 2015). The PAG assimilates information from the somatosensory and cingulate cortices, the thalamus, amygdala and hypothalamus as well as directly receiving nociceptive input from the ascending pathways. However, although there is evidence for the PAG having direct projections to the spinal cord (Mantyh and Peschanski, 1982) spinal analgesia following its stimulation is considered to be due to its projections to the nucleus raphe magnus (NRM) and neighbouring structures of the rostral ventromedial medulla (RVM) (Vanegas and Schaible, 2004; Heinricher et al., 2009). In general, the descending pathways ascendancy can be considered to originate at the periaqueductal grey-rostral ventromedial medulla (PAG-RVM) and the ventrolateral medulla (Basbaum and Fields, 1979). Within the spinal cord the descending inhibitory influences are arranged in the dorsolateral funiculi with the facilitatory influences tending to be centred in the ventral/ventrolateral cord (Zhuo & Gebhart 1997; Zhuo & Gebhart 1990). The PAG-RVM exerts a degree of selective inhibition of C fibre mediated nociceptive impulses, but preserves A fibre messages coding sensory and discriminatory information (Lu et al., 2004; McMullan and Lumb, 2006a; Heinricher et al., 2009) and the RVM can be considered the final relay point through which facilitation or inhibition of the nociceptive message passes (Villanueva and Le Bars, 1995; Calejesan et al., 2000). The degree of inhibition or facilitation of the pain signals in some part is controlled in the RVM by at least two different types of neurones known as ON-cells and OFF-cells and these cells are inextricably connected to the higher brain centres

involved in a large number of emotions, psychological states, stresses, and pathologies. The role of these cells may be more complicated than previously thought (Cleary et al., 2008; Lau and Vaughan, 2014; Salas et al., 2016). Despite the overwhelming evidence for the major role of the RVM as a relay station, it is without doubt that the descending pathways also require a forebrain loop (Millan, 2002). There is also evidence for anterior cingulate cortex (ACC) projections regulating spinal neurones (Gu et al., 2015; Kang et al., 2015) and being able to selectively modulate the pain experience. The ACC is involved in the processing and modulation of pain affect, and offers a further target for manipulating the pain signature. Understanding the role the ACC plays requires more sophisticated paradigms rather than relying primarily on the reflexive behaviour from an aversive stimulus. The role of the ACC and pain processing is comprehensively described in a recent review article (Fuchs et al., 2014). The dorsolateral and lateral sector of the midbrain PAG has differential downstream effects on the nociceptive reflexes evoked by activity in both the unmyelinated (C-fibre) and the myelinated (A-fibre) nociceptors (McMullan and Lumb, 2006a, 2006b). This differential control of nociceptive reflexes is also seen following RVM stimulation (Lu et al., 2004) demonstrating that these descending endogenous systems have A and C fibre specificity offering further complexity but nonetheless attractive targets for analgesia interventions (Waters and Lumb, 2008). In the mature adult rat, descending inhibition is targeted to spinal neurones with a strong afferent C fibre input. However, in the first few weeks postnatally the system is controlled differently, with greater descending facilitation particularly targeted to the A fibre input (Koch and Fitzgerald, 2014). The evolutionary reason proposed for this A fibre input is to provide the dorsal horn with low level, non-noxious, tactile input thereby promoting a development of the animal's sensory networks. The switch from facilitation to inhibition as the animal matures is primarily dependent on endogenous opioid levels in the RVM (Hathway et al., 2009) with GABA and endocannabinoid levels also playing a role (Hathway et al., 2012;

Li et al., 2015). It is possible that immature nervous systems could be at risk of excessive sensory overload and peripheral injury in the first few weeks of life where facilitation is favoured (Schwaller et al., 2016). In summary, this balance of inhibition and facilitation of descending pathways is a dynamic product of the afferent evoked activity, the age of the animal, but also the excitability of the dorsal horn cell too (Koch and Fitzgerald, 2014).

Notwithstanding the anatomical arrangement, the descending pathways appear to lack specificity, influencing all portions of the spinal cord and it is this widespread and intrinsic influence that is responsible for the ability to facilitate or inhibit transmission. Indeed, this widespread arrangement also results in not only pain perception being affected but other senses too, potentially explaining why some chronic pain states have clinical signs distinct from pain alone but can manifest with debilitating effects on sleep and other emotions (Tracey, 2010; Zhuo, 2016). Moreover, the perception of pain is sensitive to many mental processes therefore not exclusively driven by or maintained by the noxious input (Wiech et al., 2008); heightened anxiety and fear for example can then often exacerbate the suffering of pain (Wiech and Tracey, 2009). Human patients with mental disorder comorbidities are less likely to respond well to interventions (Dersh et al., 2002), and studies have proved the positive link between pain and anxiety, with negative emotions also being able to cause or exacerbate pain (Wiech and Tracey, 2009). To date much of the research has focussed on anxiety and depression and the expression of pain, but recently studies have also investigated anger, worry and frustration as modulators of pain (De Vlieger et al., 2006; Eccleston and Crombez, 2007; van Middendorp et al., 2010). The affective dimensions of pain are comprehensively covered elsewhere (Rainville et al., 2005). Chronic pain can impact on many cognitive domains and future research is still required to fully understand this relationship (Geisser and Kratz, 2018).

Research is also required to understand pain vulnerability and resilience in chronic pain patients and how this determines the symptoms of the sufferer and the ability to prescribe the most appropriate and efficacious rehabilitation and treatment (Denk et al., 2014).

The monoamines

The major descending pathways use the monoamines noradrenaline and 5-hydroxytryptamine (5-HT; serotonin) as transmitters (Bannister and Dickenson, 2016; Millan, 2002). These bidirectional monoaminergic systems exert a complex modulating role over the outputs of the dorsal horn neurones and the current understanding is that descending control is overwhelmingly determined by noradrenaline and serotonin activity. The inhibition or facilitation have been shown to be mediated by distinctly different receptors (Zhuo & Gebhart 1990; Zhuo & Gebhart 1990; Zhuo & Gebhart 1991), and the balance of power between the systems is determined by the type of noxious input and the response to it. The vast multiplicity of the transmitter pharmacology involved in the descending controls is comprehensively covered elsewhere (Millan, 2002).

Noradrenaline

Noradrenaline was discovered in the brain in the 1950s. It is the major neurotransmitter released by sympathetic postganglionic nerve fibres and is involved in autonomic regulation of numerous organs. In addition, noradrenaline is involved in modulating nociception (Gyires et al., 2009; Pertovaara, 2013, 2006) the majority of descending noradrenergic projections originating from the pontine nucleus locus coeruleus and microstimulation of this nucleus was shown to produce antinociceptive effects via spinal alpha 2 adrenoceptors (Jones and Gebhart, 1986). In healthy subjects the noradrenergic system plays a small part in regulating pain threshold, with its role becoming more prominent in cases of injury or inflammation

(Pertovaara, 2013). Noradrenaline released from the locus coeruleus is also involved in the regulation of vigilance, attention, and cognitive functions but it is still not possible to surmise on the net effect of the noradrenergic system on supraspinal structures; evidence exists for both anti-nociceptive and pro-nociceptive actions (Llorca-Torralba et al., 2016). However, in the main, the central noradrenergic system inhibits pain, and drugs acting on the alpha 2 adrenoceptor, alone (or as an adjuvant) have proved effective to varying degrees as analgesics, in humans and animals e.g. topically applied agonists may have a role in neuropathies (Wrzosek et al., 2015), intra-articular administration has reduced postoperative knee pain (Al-Metwalli et al., 2008) and for patients with intractable cancer pain, intrathecal administration has also been effective (Eisenach et al., 1995). The alpha 2 agonists are widely utilised in wild, domestic and laboratory animals for sedation, analgesia and muscle relaxation. Continuous rate infusions of dexmedetomidine and medetomidine can also be useful as a component of multimodal analgesic regimes during anaesthesia in horses, dogs and cats (Ansah et al., 2000; Murrell and Hellebrekers, 2005; Ringer et al., 2007; Valtolina et al., 2009; Kalchofner et al., 2009). In general, spinally administered alpha 2 adrenoceptor agonists have an enhanced antinociceptive potency in animal models with a persistent injury (Mansikka et al., 1996; Xu et al., 1999; Yaksh et al., 1995), and what is becoming clear is that the intensity, duration and type of noxious injury will ultimately determine the noradrenergic response (Poree et al., 1998; Kingery et al., 2000; Malmberg et al., 2001; Lähdesmäki et al., 2003; Mansikka et al., 2004). Likewise, abnormal noradrenergic activity (for example a reduction in the inhibitory influences) can contribute to the hypersensitivity seen in models of both acute inflammation and nerve injury (De Felice et al., 2011; Green et al., 1998; Rahman et al., 2008; Xu et al., 1999) hence the interest in the noradrenergic system as a target for analgesics. This central role is further evidenced by studies that have demonstrated restoration of diminished noradrenergic control after use of a selective noradrenaline reuptake inhibitor following the development of

a neuropathic pain phenotype (Hughes et al., 2015). In these experiments, chronic intrathecal reboxetine alleviated the evoked hypersensitivity produced by tibial nerve transection.

Serotonin/5-HT

Serotonin has a diverse and widespread distribution throughout the body and even though most serotonin is located outside of the central nervous system, it is commonly considered one of the most important neurotransmitters. Studies have shown that approximately 20% of the neurones in the RVM are serotonergic, and there was early evidence for 5-HT involvement in descending modulation (Le Bars, 1988). These descending pain modulatory pathways arising from the RVM exert a bidirectional influence upon nociception through activation of different serotonergic receptors in the spinal cord (Dogrul et al., 2009). Both acute and chronic noxious stimuli can activate these RVM 5-HT neurones and increase the expression of 5-HT receptors in the spinal cord (Cai et al., 2014; Zhang et al., 2000). The 5-HT neurones can influence nociceptive processing directly but also indirectly by influencing other non-serotonergic neurones involved in the descending pathways. The collaterals of the 5-HT neurones have been shown to regulate the bidirectional control from the aforementioned 'ON' and 'OFF' cells in the RVM (Braz and Basbaum, 2008). Unlike the adrenergic system which is largely considered a pain inhibitory system (due to the activation of alpha 2 adrenoceptors) the serotonergic/5-HT system is more complex with pain inhibition or facilitation attributable to different subtypes of 5-HT receptors (Dogrul et al., 2009; Suzuki et al., 2004; Viguier et al., 2013); 5-HT2 and 5-HT3 receptors being considered facilitatory and 5-HT7 and 5-HT2A receptors classified as inhibitory. On balance, it would seem the facilitation assumes more influence than the inhibition.

It is also now known that tonic activation of 5-HT (and non 5-HT) mediated brainstem facilitatory influences is one of a multitude of contributors to the development and maintenance of central sensitization in sustained pain states (Porreca et al., 2002; Urban and Gebhart, 1999).

Dopamine

The monoamine dopamine also plays a role in descending controls (Bannister and Dickenson, 2016) with mesolimbic, mesocortical and nigrostriatal dopaminergic pathways identified as capable of modulating (inhibiting) nociception, primarily its affective component (Gao et al., 2001; Magnusson and Fisher, 2000) more by influences in the brain rather than direct spinal projections *per se*. The dopamine system is embedded in the pain matrix circuitry (Wood, 2008) but also features importantly in the movement system (Cenci, 2007) and in areas of the brain associated with reward (Baik, 2013), learning and cognition (Robbins and Arnsten, 2009; Werlen and Jones, 2015).

Studies have shown that dopamine therapies may offer promise as analgesics (Evans et al., 2008; Park et al., 2016) and play a role in descending modulation of sensory processing (Garcá-Ramrez et al., 2014) but efforts to develop dopamine based therapies are complicated by its intrinsic role in locomotion, learning and reward.

The role of the opioids

The descending modulatory pathways can also be considered components of an opioid sensitive matrix. Many of the drugs interacting with components of the descending pathways influence or mimic the production of endogenously produced opioids, and there is evidence of a bulbospinal opioidergic pathway.

Numerous animals studies have shown that the PAG is one of the major sources of opioid mediated inhibition of the ascending nociceptive impulses (Waters and Lumb, 1997).

The PAG receives cortical inputs mediating a 'top down' endogenous pain inhibition system, and these projections from the PAG extend to the RVM and noradrenergic pontine nuclei which in turn modulate nociceptive input at the spinal cord through the aforementioned release of noradrenaline and serotonin. It is likely that the communication from the PAG to these noradrenergic and serotoninergic fibres can be both direct but also invoked through intermediate relays (Odeh and Antal, 2001). Different regions of the PAG have different functions; with respect to the descending control of pain, the dorsal-dorsolateral portions of the PAG play a role in stress-induced analgesia, which is independent of opioids but depends on endocannabinoids; the lateral-ventrolateral portions of the PAG are involved in opioid analgesia and analgesia induced by NSAIDs (Vanegas et al., 2010).

One example of this 'top down' modulating pathway is the placebo effect – an analgesic construct that can be elicited in certain people that has its mechanisms firmly rooted, but likely not limited to activation of the mu opioid receptor and changes in blood flow to these areas; particularly the rostral anterior and pregenual cingulate cortices, the dorsolateral prefrontal cortex and anterior insular cortex (Petrovic et al., 2010; Zubieta et al., 2005). In the case of placebo it is now apparent that other non-opioidergic mechanisms are also likely recruited since expectation, reward, learning and memory play a part in this response, and the once simplistic view that the mu opioid receptor was solely responsible has been superseded by a complex web of interwoven processes (Eippert et al., 2009). The recent finding that opioidergic descending pathways are also players in potential interventions such as distraction and hypnosis, offers potential for developing further analgesic interventions. Functional magnetic resonance imaging (fMRI) studies have shown (particularly in placebo and nocebo studies) that the descending pathways are the conduits through which the cognitive influences affect a pain experience. This experience is also subsequently modulated by the individual's control and on-going response to the pain experience exerted by pre-frontal limbic brain regions

(Krummenacher et al., 2010; Wiech et al., 2008). The exact mechanisms involved in the descending controls are not yet fully understood, but a consensus on their importance is without doubt and research into recruitment of their endogenous modulating attributes is a worthwhile and commendable ambition.

Other transmitters and pathways modulated by or modulating the descending controls

Endocannabinoids

There is also widespread evidence of endocannabinoid involvement in areas involved in the processing of nociceptive inputs (Jenkins et al., 2004). The expression of the endocannabinoid receptors, presence of ligands and metabolites is dynamic and dependent on the type of pain being expressed offering potentially attractive targets for analgesic opportunities (Jhaveri et al., 2007; Sagar et al., 2009) but it is also involved in motor function, cognition, and many signalling pathways, making isolation of the analgesic properties of molecules without psychoactive side effects a challenging conundrum. It has been shown that analgesia produced by NSAIDs in the descending pain control system also requires an activation of the CB1 endocannabinoid receptor (Vanegas et al., 2010). Furthermore, numerous experiments suggest that opioids, NSAIDs and the cannabinoids in the PAG and RVM interact to potentially decrease gamma-aminobutyric acid (GABA)-ergic inhibition and thus enhance the descending flow of impulses that inhibit pain as a mechanism of analgesia (Tham et al., 2005; Guindon et al., 2006; Guindon and Hohmann, 2009)

There is also evidence that the endocannabinoid system can express adaptive changes in the face of persistent pain states such as osteoarthritis (Sagar et al. 2010) highlighting one of the many potential systems to target in the face of spinal hyperexcitability.

GABA and glycine

Electrophysiological studies have also highlighted a major role for GABA and glycine as inhibitory transmitters through their ability to influence descending activity via their presence within interneurones. Projections from the PAG also synapse with GABAergic spinopetal neurones. These GABAergic or glycinergic projections can inhibit noxious inputs into the dorsal horn of the spinal cord, and recent elegant tracer studies have identified that the neurones can express either or both neurotransmitters (Hossaini et al., 2012). Their role in modulating the noxious input is without doubt but parsing out the exact role of each system and how they interact remains unfinished. Studies have also demonstrated that the ON, OFF and neutral cells have varying expression of GABA and glycine, but globally the cell populations and expression is determined by the context of the pain experience; for example in peripheral inflammation the gene expression and the phenotype of the ON and OFF cells was altered (Miki et al., 2002). This study demonstrated during continuous neuronal recordings (3–6.5 h), a phenotypic switch of RVM neurones during the development of inflammation. This was characterised by an increase in the percentage of ON and OFF cells and a reduction in the percentage of neutral cells, and this phenotypic change was mediated via NMDA receptor activation in response to the inflammation (Miki et al., 2002).

Tonic control

In the absence of nociceptive input spinal nociceptive neurones are under both tonic and stimulus evoked descending controls (Gilbert and Franklin, 2001; Sandkuhler et al., 1987). Some of the evidence for the tonic control comes from studies investigating the development of long term potentiation (LTP) as a model for central sensitization. LTP can be induced in anaesthetized rodents by stimulating the spinal dorsal horn neurones with high intensity electrical pulses and the effect is manifest as an increased postsynaptic response to a single

stimulus applied to the afferent once a minute. The stimulus used is not representative of a natural noxious stimulus, and indeed it is very challenging to elicit LTP in natural circumstances. However, in animals that have undergone rostral spinalization, LTP could be induced with natural noxious stimuli such as pinch or intense heat. In these cases this is allied to primary hyperalgesia and illustrates that spinalization has removed the tonic descending inhibitory control (Sandkühler and Liu, 1998). The structures responsible for tonic descending inhibition can be probed by destroying the descending serotonergic neurones of the NRM and comparing the paw inflammation and withdrawal responses in these lesioned rats compared to the normal rats and hyperalgesia was more marked in these rats lesioned 4-14 days earlier (Ren and Dubner, 1996). Locus coeruleus lesions also result in an increased hyperalgesia caused by carrageenan compared to non-lesioned rats confirming again the loss of tonic descending control (Tsuruoka et al., 2004). Characterization of the receptors involved in the tonic control mechanisms has also been shown through many elegant experiments using antagonists (Clarke and Harris, 2004; Rivot et al., 1987; Soja and Sinclair, 1983). One important caveat to these experiments involving discrete lesions and anaesthesia is they may inadvertently overlook the contribution of the plasticity of the spinal cord in response to inflammation or indeed the differences in the free ranging conscious animal compared to anaesthetized animal, and these should be considered when drawing conclusions.

Conditioned pain modulation (CPM) and Diffuse Noxious Inhibitory Control (DNIC)

Normally in healthy naïve animals and humans, a conditioning noxious stimulus will attenuate the response to a test stimulus applied to a remote (extra segmental) body area, a phenomenon termed diffuse noxious inhibitory control, (DNIC) (Le Bars et al., 1979) or ‘pain inhibiting pain’. DNIC are powerful, long-lasting controls which inhibit spinal as well as trigeminal nociceptive neurones (Dallel et al., 1999; Dickenson et al., 1980). DNIC operate

via a loop with the afferent and efferent pathways coursing through the ventrolateral quadrant and the dorsolateral funiculus of the spinal cord (Villanueva and Le Bars, 1995). Early experiments have demonstrated that sectioning the spinal cord abolishes DNIC, with supra-spinal areas such as the caudal medulla and the subnucleus reticularis dorsalis (SRD) involved (Bouhassira et al., 1992) and with the spinoparabrachial and the hypothalamic dopaminergic descending pathways facilitating the ascending and descending components of the loop (Lapirot et al., 2011, 2009). The monoamines play pivotal roles in DNIC and offer potentially attractive targets for interventions (Bannister et al., 2015; Harris, 2016; Lebars, 1979).

What has become apparent across many different persistent painful conditions (e.g. migraine, irritable bowel disease, and idiopathic pain states) is that some humans have been shown to have impaired DNIC (Yarnitsky, 2010) thereby suggesting that a DNIC paradigm could be used in prediction of chronic pain susceptibility (van Wijk and Veldhuijzen, 2010). As previously mentioned the descending pathways consist of inhibitory and facilitatory controls; experimentally these opposing pathways can be studied, but in a patient, currently it is only possible to infer the aggregate of the descending control, and so the DNIC terminology has been superseded by Conditioned Pain Modulation (CPM) for humans. CPM describes the phenomenon by which a conditioning stimulus affects the test stimulus, and can be further subdivide into non painful, inhibitory and facilitatory CPM (Yarnitsky et al., 2010a). Employing CPM tools in human pain research is still in its infancy, but reliability and consensus on testing is available (Nir and Yarnitsky, 2015; Yarnitsky et al., 2015). For both client owned animals and laboratory animals, there are only a very small number of studies published evaluating DNIC, as the methodology is defined and refined in view of the fact that the effect of sedation or anaesthesia must be considered because of the necessity to apply a potentially aversive stimulus (Hunt et al., 2016; White et al., 2017). It is likely that evaluation of domestic animals suffering from chronic pain will evolve to include but not be limited to

tests of CPM, central sensitization (defined as the reversible increase in excitability of neurones in the central nociceptive pathways and manifest as altered pain sensitivity that can be measured with quantitative sensory testing), peripheral sensitization (measured with tools evaluating allodynia and hyperalgesia) and more comprehensive ethograms. Furthermore, tests that can evaluate spontaneous pain behaviours are desirable, in addition to being able to assess the complex relationship between chronic pain and quality of life through aspects of sleep, mood, cognitive ability, appetite and the negative affect (Mogil, 2009). Despite all of these challenges in the non-verbal species, there is more need than ever to correlate the altered pain phenotypes that occur in pain states in domestic animals with these clinical behaviours to ensure therapy is targeted and efficacious and pain interventions can be better developed.

Delivering Clinical Impact

The exact role of the descending pathways and downstream transmitters for different pain states has yet to be confirmed but consensus is that progress in these areas will lead to improvements in pain management. For example, for osteoarthritis (OA), a chronic debilitating disease in humans and animals, the treatment remains an unmet need and this is likely due to the disease being driven not only by peripheral sensitizing inputs but also by a central component. This central sensitization is believed to be responsible for altering the balance in the serotonergic and noradrenergic pathways originating in the PAG-RVM and increasing the barrage of nociceptive impulses reaching the brain resulting in increased pain. Pre-clinical OA studies have demonstrated an increased serotonergic facilitation in the descending pathways resulting in increased spinal cord hyperexcitability (Rahman et al., 2009) but also some of the aforementioned transmitters such as the endocannabinoids are also altered (Sagar et al., 2010). In the vast majority of painful disease states, damage to tissue and/or nerves in the periphery is the inciting cause, leading to enhanced transmitter release in the spinal cord and central

sensitization. The central sensitization is then maintained by continuing input from the periphery with modulation from inhibitory and facilitatory descending control from the midbrain and brainstem. In many cases it is difficult to parse out the degree of central or peripheral input so to effectively treat the disease, both the peripheral input and the central modulation will need to be addressed to effectively improve the patient's quality of life.

Descending controls in acute and chronic pain

Following even brief injury or noxious stimulation the descending inhibitory pathways from the RVM or ACC may be recruited; functionally offering an injured animal an evolutionary advantage for example, escaping from a predator. The role of the descending facilitation is less clear from both an evolutionary and functional context compared to inhibition but maintaining a degree of secondary hyperalgesia as injured tissue heals could be beneficial to avoid ongoing damage to the affected area. Descending facilitation is easier implicated in abnormal pain states (Wang et al., 2013). This facilitation also seems likely to be responsible for the maintenance but not the initiation of neuropathic pain (D'Mello and Dickenson, 2008) and is supported by studies evaluating the time course of nerve induced hypersensitivity (Burgess et al., 2002; Vera-Portocarrero et al., 2006).

Not all animals or humans with persistent disease will go onto develop chronic pain. Predicting which patients will suffer is not straightforward, neither is it an inevitability. There are subsets of human patients who are more at risk of developing persistent pain states but reliably identifying them is challenging, nonetheless an incredibly important paradigm to develop (Denk et al., 2014). In many chronic pain states, there is compelling evidence that the sustained debilitating effects of the pain are fuelled by inappropriate activity in the descending pathways since the pain intensity is often mismatched by the degree of pathology or in widespread pain states where the inciting cause is still unclear. From a clinical standpoint in humans, the ability

to identify patients with impaired DNIC/CPM can then result in a more rapid and efficacious treatment plan tailored to the individual, targeting the impaired descending pathways (Arendt-Nielsen and Yarnitsky, 2009; Yarnitsky et al., 2010b). It has been shown that in patients suffering from diabetic neuropathy, the baseline CPM correlated with efficacy of the selective serotonin-norepinephrine reuptake inhibitor (SSNRI) duloxetine (Yarnitsky et al., 2012). DNIC/CPM testing has been shown to be predictive of developing chronic post-operative pain for patients undergoing surgery for knee replacement (Petersen et al., 2016) and following thoracotomy (Yarnitsky et al., 2008). Altered CPM has also been identified in patients with migraine, chronic tension type headaches, medication overuse headache and headache following traumatic brain injury too (Pielsticker et al., 2005; Perrotta et al., 2010, 2013; Defrin, 2014). Moreover, in one study of cluster type headache, DNIC inhibition was absent during the active phase of the disease and evident in the remission phase confirming DNIC dysfunction (Perrotta et al., 2013); although whether this is a primary DNIC dysfunction or hypothalamic in origin is unknown. Currently assessing DNIC/CPM in veterinary patients is uncommon but potentially offers similar benefits to human patients in order to hone treatment and improve quality of life.

Conclusions

The descending control of the spinal nociception has evolved from a simplistic construct of the supraspinal and segmental influences having a direct effect on the sensory processes and being able to influence the acute or chronic pain experience. We now consider a more complex Bayesian matrix where the nociceptive input will be concurrently constrained by behavioural/learned/predicted and homeostatic mechanisms as well as the peripheral incoming signals.

In conclusion, what we do know is that dynamic shifts in the descending controls alter the gain in the processing of nociceptive inputs against the background of experiences, emotions and input from the limbic brain. Better understanding of these descending mechanisms will surely equip us not only to modulate the persistent pain experience but also to design therapies to provide an improved quality of life for both animals and humans.

Conflict of interest statement

None of the authors of this paper has a financial or personal relationship with other people or organisations that could inappropriately influence or bias the content of the paper.

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Figure Legends

Figure 1

Schematic diagram of pain pathway from periphery to brain including sagittal midline T2 weighted MRI images from a dog brain with selected transverse images at the level of the (1) thalamus, (2) midbrain and (3) rostral medulla annotated to indicate the anatomical localisation of regions involved in descending modulation

Primary afferent fibres (A-beta, A-delta, and C-fibres) transmit impulses from the periphery (osteoarthritic hip joint) to the dorsal horn of the spinal cord. Secondary nociceptive specific cells (NS) are predominantly located in the superficial dorsal horn (laminae I–II), with most wide dynamic range (WDR) neurones located in the deeper dorsal horn (e.g. lamina V). Lamina V neurones in particular project to the thalamus (via the spinothalamic tract) where there are subsequent neuronal projections to various cortical regions which form part of a 'pain matrix' (primary and secondary somatosensory, insular, anterior cingulate, and prefrontal cortices). The descending pathways originate from brainstem nuclei such as the rostral ventromedial medulla (RVM) and the locus coeruleus (LC) which are directly influenced by the ascending spinobulbar projections and higher centres to modulate spinal processing.

PAG: periaqueductal grey, DRG: dorsal route ganglion, RVM: rostroventromedial medulla, LC: locus coeruleus, LS: limbic system, NS: nociceptive specific cells, PB: parabrachial nucleus, WDR: wide dynamic range neurones